EXHIBIT 38

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Obesity and risk of ovarian cancer subtypes: evidence from the Ovarian Cancer Association Consortium

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Abstract

Whilst previous studies have reported that higher BMI increases a woman's risk of developing ovarian cancer, associations for the different histological subtypes have not been well defined. As the prevalence of obesity has increased dramatically, and classification of ovarian histology has improved in the last decade, we sought to examine the association in a pooled analysis of recent studies participating in the Ovarian Cancer Association Consortium. We evaluated the association between BMI (recent, maximum and in young adulthood) and ovarian cancer risk using original data from 15 case–control studies (13 548 cases and 17 913 controls). We combined study-specific adjusted odds ratios (ORs) using a random-effects model. We further examined the associations by histological subtype, menopausal status and post-menopausal hormone use. High BMI (all time-points) was associated with increased risk. This was most pronounced for borderline serous (recent BMI: pooled OR = 1.24 per 5 kg/m^2; 95% CI 1.18–1.30), invasive endometrioid (1.17; 1.11–1.23) and invasive mucinous (1.19; 1.06–1.32) tumours. There was no association with serous invasive cancer overall (0.98; 0.94–1.02), but increased risks for low-grade serous invasive tumours (1.13, 1.03–1.25) and in pre-menopausal women (1.11; 1.04–1.18). Among post-menopausal women, the associations did not differ between hormone replacement therapy users and non-users. Whilst obesity appears to increase risk of the less common histological subtypes of ovarian cancer, it does not increase risk of high-grade invasive serous cancers, and reducing BMI is therefore unlikely to prevent the majority of ovarian cancer deaths. Other modifiable factors must be identified to control this disease.

Key Words
- ovarian cancer
- obesity
- BMI

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Introduction

It is widely accepted that being overweight or obese increases a woman's risk of developing endometrial and post-menopausal breast cancer (Calle & Kaaks 2004). The association with ovarian cancer is less clear, largely because individual studies have had insufficient power to reliably detect moderate effects or to consider the different histological subtypes of ovarian cancer. In 2008, a pooled analysis of cohort studies concluded that BMI was associated with ovarian cancer in pre-menopausal women only, however this analysis only included 2000 cases and thus also had limited power to evaluate the different histological subtypes separately (Schouten *et al.* 2008). A recent pooled analysis conducted to overcome these limitations concluded that among women who have not used hormone replacement therapy (HRT), the risk of ovarian cancer increases by 10% for every 5 kg/m^2 increase in BMI (Collaborative Group on Epidemiological Studies of Ovarian Cancer 2012). This association did not vary significantly for the different histological subtypes of ovarian cancer, with the exception of borderline serous cancers where the excess relative risk (RR) was substantially greater than for the other tumour types. There was no increase in risk with increasing BMI among women who had used HRT.

However, the mean year of diagnosis of the cases in the studies included in the previous report was 1992 (Collaborative Group on Epidemiological Studies of Ovarian Cancer 2012) and over the last few decades, most countries have seen dramatic increases in the prevalence of overweight and obesity (Finucane *et al.* 2011). Classification of the different histological subtypes of ovarian cancer has also improved in recent years (Gilks & Prat 2009) and it is possible that misclassification in earlier studies might have masked differences between the histological subtypes. In particular, it is now recognised that low- and high-grade invasive serous cancers are distinct entities and that many cancers previously described as high-grade endometrioid tumours should really be classified as high-grade serous cancers (Gilks & Prat 2009). We therefore sought to confirm the results of the previous analysis in a second, independent pooled analysis using data from more recent studies that met the inclusion criteria for the Ovarian Cancer Association Consortium (OCAC) collaboration (Ramus *et al.* 2008).

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We examined the associations by histological subtype and tumour grade and by menopausal status and HRT use because, if the effects of obesity on ovarian cancer risk are mediated through oestrogenic pathways, then any association between BMI and risk may be more evident among women who have not used exogenous oestrogens. We also evaluated the relation between body size at different ages and ovarian cancer risk.

Materials and methods

OCAC was founded in 2005 to foster collaborative efforts in discovering and validating associations between genetic polymorphisms and ovarian cancer risk. A detailed description has been provided elsewhere (Ramus *et al.* 2008) but, briefly, studies were eligible for inclusion if they included at least 200 cases of ovarian cancer and 200 controls, with controls from broadly the same population as cases, and provided DNA for genetic analyses. Table 1 summarizes the characteristics of the 15 case–control studies (14 population-based and one clinic-based) that provided data for these analyses (Ziogas *et al.* 2000, Royar *et al.* 2001, Glud *et al.* 2004, Pike *et al.* 2004, Hoyo *et al.* 2005, Terry *et al.* 2005, Risch *et al.* 2006, Garcia-Closas *et al.* 2007, Rossing *et al.* 2007, Kelemen *et al.* 2008, Lurie *et al.* 2008, Merritt *et al.* 2008, Moorman *et al.* 2008, Wu *et al.* 2009, Balogun *et al.* 2011, Bandera *et al.* 2011, Ness *et al.* 2011). Race/ethnicity was categorised as non-Hispanic White (88%), Hispanic White (3%), Black (4%), Asian (3%) or other (2%). All studies had ethics approval, and all study participants provided informed consent.

Analysis variables

There was some variation in the way weight information was collected by the individual studies (Supplementary Table 1, see section on supplementary data given at the end of this article). Weight in early adulthood was reported by 14 studies (all except MAY); this was reported as weight at age 18 for nine studies and at age 20 for two studies (AUS and GER), while three studies reported weight 'in your 20s' (CON, MAL and USC). Recent weight was reported by 11 studies (AUS, CON, DOV, HOP, MAL, MAY, NCO, NJO, NEC, UCI and USC); for most studies this was reported as weight 1 year prior to diagnosis/reference date, but 5 years prior to diagnosis/reference date was used for four studies (CON, DOV, MAL and USC). To minimise overlap between our analyses of recent weight and the previous pooled analysis (The Collaborative Group on Epidemiological Studies of Ovarian Cancer 2012), we excluded two studies (GER and HAW) that were included in the previous analysis, but included two studies (NEC and USC) that had contributed only part of their data to the previous analysis (total overlap ~1200 cases). Maximum weight was reported by eight studies (AUS, DOV, GER, HAW, HOP, NCO, NJO and POL). BMI, calculated as weight in kilograms divided by the square of height in metres (kg/m^2), was classified using the WHO definitions of obesity (<18.5 'underweight'; 18.5–24.9 'normal weight'; 25–29.9 'overweight'; 30–34.9 'class I obesity'; 35–39.9 'class II obesity' and ≥40 'class III obesity'; WHO 1995). For subgroup analyses there were small numbers in the upper classes of obesity for BMI in early adulthood, so these groups were combined.

Covariate information

Each case–control study provided information on potential confounding variables including age, cancer grade, race/ethnicity, parity, breastfeeding, oral contraceptive (OC) and HRT use, family history of breast or ovarian cancer in a first-degree relative, menopausal status and history of hysterectomy or tubal ligation. All data were cleaned and checked for internal consistency and clarification was provided by the original investigators when needed.

Statistical analysis

We used Stukel's two-stage method of analysis to obtain study-specific odds ratios (ORs) and pooled ORs (pORs) and 95% CIs (Stukel *et al.* 2001). In the first stage, each study was analysed separately, controlling for study-specific confounders. The pooled exposure effect was estimated in a second stage using a meta-analytic approach. A weighted average of the log RR was estimated, taking into account the random effects using the method of DerSimonian & Laird (1986). Statistical heterogeneity among studies was evaluated using Cochran's Q-test and I^2 statistics (Higgins & Thompson 2002). All models were stratified by age in 5-year groups and adjusted for parity (0, 1, 2, 3, 4+ full-term births), OC use (0, ≤60 and >60 months) and family history of breast or ovarian cancer in a first-degree relative. We also adjusted study-specific results for race/ethnicity (non-Hispanic White, Hispanic White, Black, Asian and other) where more than 10% of the study population was not classified as non-Hispanic White and inclusion of a term for race/ethnicity altered the OR by 10% or more. Other potential confounders considered but not included in final models since they did not make any material change to the BMI associations

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Table 1 Characteristics of the 15 studies included in the pooled analyses of BMI and ovarian cancer.

Study	Diagnosis (years)	Age (range)	Geographic location	Number of: Cases[a]	Number of: Controls[a]	Control sources (response rate)	Histology: Invasive cases (%)	Histology: Borderline cases (%)	Control sources (response rate)	BMI measurement: Recent	BMI measurement: Early adulthood	BMI measurement: Maximum
Clinic-based												
Mayo Clinic Ovarian Cancer Case Control Study (MAY)	2000–2008	20–91	Upper Midwest, USA	715	945	Mayo Clinic (84%)	Ser 405 (57%) Muc 19 (3%) End 100 (14%) CC 44 (6%) Other 47 (7%)	Ser 59 (8%) Muc 27 (4%) Other 14 (2%)	Women seeking general examinations (65%)	Y		
Population-based												
Australian Ovarian Cancer Study and Australian Cancer Study (Ovarian Cancer; AUS)	2002–2006	18–80	Australia	1579	1485	Cancer registries, treatment centres (84%)	Ser 756 (48%) Muc 49 (3%) End 150 (9%) CC 98 (6%) Other 192 (12%)	Ser 150 (9%) Muc 169 (11%) Other 15 (1%)	Electoral roll (47%)	Y	Y	Y
Connecticut Ovary Study (CON)	1998–2003	34–81	Connecticut, USA	483	551	Cancer registries, pathology departments (69%)	Ser 221 (46%) Muc 19 (4%) End 74 (15%) CC 35 (7%) Other 25 (5%)	Ser 69 (14%) Muc 36 (7%) Other 4 (1%)	Random digit dialling (61%)	Y	Y	
Diseases of the Ovary and their Evaluation Study (DOV)	2002–2005	35–74	Washington, USA	1569	1848	Cancer Surveillance System, SEER (77%)	Ser 672 (43%) Muc 33 (2%) End 187 (12%) CC 87 (6%) Other 176 (11%)	Ser 234 (15%) Muc 156 (10%) Other 24 (2%)	Random digit dialling (69%)	Y	Y	Y
German Ovarian Cancer Study (GER)	1993–1998	21–75	Germany	254	519	Hospital admissions (58%)	Ser 106 (42%) Muc 26 (10%) End 26 (10%) CC 6 (2%) Other 63 (25%)	Ser 15 (6%) Muc 9 (4%) Other 3 (1%)	Population registries (51%)		Y	Y
Hawaii Ovarian Cancer Study (HAW)	1993–2008	18–93	Hawaii, USA	883	1089	Cancer registry (78%)	Ser 312 (35%) Muc 70 (8%) End 116 (13%) CC 81 (9%) Other 122 (14%)	Ser 88 (10%) Muc 87 (10%) Other 7 (1%)	Department of Health Annual Survey (80%)		Y	Y
Hormones and Ovarian Cancer Prediction (HOP)	2003–2009	25–80	New York, Ohio and Pennsylvania, USA	771	1803	Cancer registries, pathology databases, physician offices (69%)	Ser 364 (47%) Muc 36 (5%) End 97 (13%) CC 52 (7%) Other 125 (16%)	Ser 58 (8%) Muc 29 (4%) Other 10 (1%)	Random digit dialling (81%)	Y	Y	Y
The Danish Malignant Ovarian Tumour Study (MAL)	1994–1999	35–79	Denmark	744	1552	Danish Cancer Registry, 16 gynaecologic departments 79%)	Ser 337 (45%) Muc 50 (7%) End 75 (10%) CC 43 (6%) Other 39 (5%)	Ser 103 (14%) Muc 87 (12%) Other 10 (1%)	Danish Central Population Register (67%)	Y	Y	
North Carolina Ovarian Cancer Study (NCO)	1999–2007	20–75	North Carolina, USA	1087	1083	North Carolina Central Cancer Registry (70%)	Ser 470 (43%) Muc 43 (4%) End 138 (13%) CC 88 (8%) Other 122 (11%)	Ser 155 (14%) Muc 64 (6%) Other 5 (0%)	Random digit dialling (63%)	Y	Y	Y
New England-based Case–Control Study of Ovarian Cancer (NEC)	1992–2008	18–78	New England, USA	1960	2097	Hospital tumour boards, State cancer registries (72%)	Ser 819 (43%) Muc 89 (5%) End 296 (16%) CC 192 (10%) Other 70 (4%)	Ser 242 (13%) Muc 145 (8%) Other 35 (2%)	Random digit dialling and townbook selection (69%)	Y	Y	
New Jersey Ovarian Cancer Study (NJO)	2004–2008	23–96	New Jersey, USA	224	448	NJ State Cancer Registry (47%)	Ser 129 (58%) Muc 11 (5%) End 31 (14%) CC 30 (13%) Other 23 (10%)		Random digit dialling, Medicare and Medicaid lists, area sampling (40%)	Y	Y	Y
Polish Ovarian Cancer Study (POL)	2001–2003	24–74	Poland	283	1071	Hospitals in Warsaw and Lodz (71%)	Ser 116 (41%) Muc 19 (7%) End 39 (14%) CC 10 (4%) Other 78 (28%)	Ser 17 (6%) Muc 3 (1%) Other 1 (0%)	Electoral roll (67%)		Y	Y

Table 1 *Continued*

Study	Diagnosis (years)	Age (range)	Geographic location	Number of:		Control sources (response rate)	Histology		Control sources (response rate)	BMI measurement		
				Cases[a]	Controls[a]		Invasive cases (%)	Borderline cases (%)		Recent	Early adulthood	Maximum
UC Irvine Ovarian Cancer Study (UCI)	1994–2004	18–86	Orange and San Diego counties, USA	588	565	Orange County Cancer Surveillance Program, Tumour Registry (70%)	Ser 211 (36%) Muc 28 (5%) End 72 (12%) CC 37 (6%) Other 43 (7%)	Ser 122 (21%) Muc 74 (13%) Other 1 (0%)	Random digit dialling (80%)	Y	Y	
UK Ovarian Cancer Population Study (UKO)	2006–2010	50–76	UK	687	1026	Gynaecologic oncology NHS centres (86%)	Ser 348 (51%) Muc 69 (10%) End 106 (15%) CC 65 (9%) Other 99 (14%)		Post-menopausal women participating in UKCTOPCS[b] (97%)		Y	
Los Angeles County Case–Control Studies of Ovarian Cancer (USC)	1993–2009	19–86	Los Angeles, USA	1721	1831	Cancer Surveillance Program of Los Angeles (73%)	Ser 826 (48%) Muc 112 (7%) End 183 (11%) CC 87 (5%) Other 110 (6%)	Ser 240 (14%) Muc 158 (9%) Other 5 (0%)	Neighbourhood controls (73%)	Y	Y	

Ser, serous; Muc, mucinous; End, endometrioid; CC, clear cell; other includes both 'other' histologies and subjects with unknown histology.
[a]Numbers of participants with body-size information.
[b]United Kingdom Collaborative Trial of Ovarian Cancer Screening.

were breastfeeding, history of hysterectomy, tubal ligation, menopausal status and HRT. Adjusting for history of endometriosis made no material change to the pooled estimates for the endometrioid or clear cell subtypes and thus it was not included in final models. Data on smoking status were not available for all studies, however including smoking status in models where it was available did not result in significant changes to the pooled estimates and thus it was not included in final models. Covariate data were mostly complete and uniformly coded for all studies with a few exceptions. The parity variable included all full-term births (live and still births) for all studies except MAY which recorded only live births. Secondly, tubal ligation and breastfeeding data were unavailable for the MAY study. These missing covariates were therefore not included in the first-stage models for this study.

We initially computed ORs for each of the primary exposure variables for invasive and borderline cancers separately and then further classified tumours by their histological subtype (serous, mucinous, endometrioid and clear cell). In the subtype-specific models, adjacent levels of confounders were collapsed where necessary to avoid zero cells in the two-stage models. Where heterogeneity was evident, we examined the data for potential sources of this heterogeneity including type of control group (population vs hospital-based) and style of questionnaire (self-completed vs in-person interview). The RR of ovarian cancer per 5 kg/m^2 increase in BMI was estimated by fitting a log-linear trend across categories of BMI (18.5–<20, 20−, 22.5−, 25−, 27.5−, 30−, 32.5−, 35−, 37.5−, 40+ kg/m^2) using the overall median value within each category, except for the top category where we used the site-specific median as this varied between sites. Since we were interested in the effects of being overweight and speculated that the relation between BMI and cancer risk might not be linear at very low BMI levels, these analyses excluded women in the 'underweight' range (BMI <18.5 kg/m^2).

We also conducted subgroup analyses to assess the interaction between recent BMI, menopausal status and use of any HRT (pre-/peri-menopausal, post-menopausal and never used HRT, post-menopausal and had used HRT). There was some heterogeneity in how menopausal status was defined across studies, so we also conducted analyses stratified by age at diagnosis (<50 and ≥50 years). To avoid problems with zero cells in some studies in these and other subgroup analyses, we pooled all data and computed ORs using logistic regression stratified by study site and age in 5-year groups in order to maximise the statistical power. The statistical significance of any observed

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stratum-specific differences was then assessed by including a cross-product term (using the continuous BMI variables defined above) in regression models.

Analyses were conducted using SAS (SAS Institute, Cary, NC, USA) and Stata 10 (College Station, TX, USA).

Results

Eleven studies contributed to analyses of recent BMI, eight studies for maximum BMI and 14 studies for BMI in early adulthood (Table 1). Using the two-stage method of analysis, we observed significantly increased risks of both invasive and borderline ovarian cancers associated with higher BMI at all three time-points. The association was modest for invasive tumours with an increase in risk of 4% per 5 kg/m^2 for recent BMI and 8% for BMI in early adulthood, but was stronger for borderline tumours with increases of 15–18% per 5 kg/m^2 for the different time-points (Table 2).

Results of the pooled analyses stratified by histological subtype are presented in Tables 3 and 4 for invasive and borderline tumours respectively. Overall, risk of invasive serous cancer was not associated with any measure of BMI (Table 3). However, stratification by tumour grade (data available for 91% of cases) revealed positive associations between all measures of BMI and risk of low-grade (G1) invasive serous tumours (OR=1.13, 1.18 and 1.24 per 5 kg/m^2 for recent, maximum and young adult BMI respectively, all $P<0.01$) but not high-grade (G2–G4) tumours (OR=0.96, 0.96 and 0.98 respectively). Higher BMI (all BMI variables) was significantly associated with an increased risk of invasive endometrioid ovarian cancer. This association was restricted to low- and intermediate-grade (G1 and G2) tumours (OR per 5 kg/m^2 1.25, 1.22 and 1.20 for recent, maximum and young adulthood BMI respectively, all $P\leq0.001$) and was not seen for high-grade (G3 and G4) endometrioid cancers (OR=0.97, 1.02 and 0.90 respectively) (data on grade available for 93% of cases). The associations between BMI and invasive mucinous and clear cell cancers were less clear, with increased risks of both tumour types associated with high recent BMI and, for mucinous cancers, BMI in young adulthood, but not maximum BMI. The results for recent BMI were essentially unaltered when we restricted the

Table 2 Adjusted[a] pooled ORs (95% CIs) for ovarian cancer in relation to BMI, by tumour behaviour[b].

	Invasive					Borderline				
BMI (kg/m^2)	Studies	I^2 (%)	Cases	Controls	pOR (95%CI)	Studies	I^2 (%)	Cases	Controls	pOR (95%CI)
Recent BMI										
<18.5	11	26.6	183	282	1.08 (0.84–1.39)	10	0.0	57	281	1.13 (0.82–1.55)
18.5–24.9 (ref)	11		4020	6796	1.0	10		1080	6599	1.0
25–29.9	11	31.2	2500	4077	1.00 (0.92–1.09)	10	13.8	662	3930	1.23 (1.09–1.39)
30–34.9	11	0.0	1166	1808	1.06 (0.97–1.16)	10	1.1	379	1741	1.61 (1.40–1.85)
35–39.9	11	1.7	511	692	1.21 (1.07–1.38)	10	0.0	150	672	1.68 (1.37–2.06)
≥40	11	0.0	383	503	1.22 (1.05–1.41)	9	0.0	137	486	1.96 (1.57–2.46)
Per 5 kg/m^2[c]	11	47.7			1.04 (1.00–1.08)*	9	0.0			1.18 (1.14–1.23)
Maximum BMI										
<18.5	6	0.0	24	33	1.22 (0.69–2.14)	3	0.0	5	19	1.00 (0.33–3.03)
18.5–24.9 (ref)	8		1393	2683	1.0	7		296	2548	1.0
25–29.9	8	6.2	1427	2566	1.02 (0.92–1.13)	7	19.7	275	2409	1.13 (0.91–1.41)
30–34.9	8	0.0	823	1335	1.17 (1.04–1.31)	7	17.0	199	1236	1.58 (1.24–2.03)
35–39.9	8	60.2	388	592	1.29 (0.99–1.68)*	6	0.0	105	544	1.70 (1.30–2.22)
≥40	8	15.9	310	490	1.16 (0.96–1.41)	5	30.5	108	455	1.90 (1.35–2.68)
Per 5 kg/m^2[c]	8	45.3			1.06 (1.01–1.11)	7	35.8			1.17 (1.08–1.26)
BMI early adulthood										
<18.5	14	0.0	1646	2931	0.94 (0.88–1.01)	12	13.0	416	2718	0.97 (0.85–1.11)
18.5–24.9 (ref)	14		7278	12 364	1.0	12		1819	11 245	1.0
25–29.9	14	0.0	788	1151	1.12 (1.01–1.24)	11	0.0	248	983	1.27 (1.09–1.49)
30–34.9	14	0.0	176	233	1.21 (0.98–1.49)	10	0.0	66	210	1.32 (0.98–1.78)
≥35	12	0.0	76	108	1.08 (0.78–1.49)	10	0.0	43	100	1.86 (1.25–2.78)
Per 5 kg/m^2[c]	14				1.08 (1.03–1.14)	12				1.15 (1.08–1.24)

*Significant heterogeneity noted (P value for heterogeneity <0.05).
[a]Stratified by age in 5-year groups and adjusted for parity (0, 1, 2, 3, 4+ full-term births), hormonal contraceptive use (0, ≤60 and >60 months), family history of breast or ovarian cancer in a first-degree relative and, where appropriate, race/ethnicity.
[b]Numbers may not sum to total because of missing data.
[c]Excludes women in the underweight range (BMI <18.5 kg/m^2).

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Table 3 Adjusted[a] pooled ORs (95% CIs) for invasive ovarian cancer in relation to BMI, by histological subtype[b].

			Serous		Mucinous		Endometrioid		Clear cell	
	Studies (*n*)	**Controls** (*n*)	Cases (*n*)	pOR (95% CI)	Cases (*n*)	pOR (95% CI)	Cases (*n*)	pOR (95% CI)	Cases (*n*)	pOR (95% CI)
Recent BMI	11									
<18.5		282	91	0.93 (0.72–1.20)	19	2.48 (1.03–4.51)	33	1.47 (0.98–2.21)	18	2.69 (1.34–5.41)
18.5–24.9 (ref)		6796	2475	1.0	207	1.0	592	1.0	353	1.0
25–29.9		4077	1477	0.93 (0.86–1.02)	134	1.19 (0.95–1.50)	380	1.12 (0.96–1.30)	227	1.05 (0.79–1.40)*
30–34.9		1808	665	0.94 (0.84–1.05)	68	1.48 (0.92–2.37)*	205	1.37 (1.14–1.64)	98	1.14 (0.79–1.63)*
35–39.9		692	275	1.06 (0.90–1.23)	29	2.03 (1.10–3.77)	97	1.74 (1.36–2.23)	48	1.59 (1.14–2.24)
≥40		503	170	0.89 (0.74–1.08)	29	2.70 (1.76–4.16)	82	1.86 (1.42–2.24)	37	1.58 (1.04–2.40)
Per 5 kg/m^2[c]				0.98 (0.94–1.02)		1.19 (1.06–1.32)		1.17 (1.11–1.23)		1.06 (0.96–1.17)*
Maximum BMI	8									
18.5–24.9 (ref)		2683	793	1.0	86	1.0	177	1.0	120	1.0
25–29.9		2566	787	0.93 (0.73–1.17)*	84	1.22 (0.88–1.69)	194	1.20 (0.96–1.45)	112	0.95 (0.72–1.26)
30–34.9		1335	445	1.03 (0.89–1.18)	34	1.08 (0.70–1.67)	129	1.63 (1.26–2.10)	69	1.22 (0.88–1.70)
35–39.9		592	199	1.18 (0.81–1.72)*	20	1.30 (0.74–2.27)	67	1.78 (1.29–2.46)	33	1.30 (0.84–2.00)
≥40		490	147	0.98 (0.68–1.41)*	17	1.37 (0.76–2.46)	60	1.82 (1.29–2.56)	27	1.12 (0.70–1.82)
Per 5 kg/m^2[c]				1.00 (0.93–1.07)		1.05 (0.94–1.17)		1.18 (1.09–1.28)		1.04 (0.95–1.13)
Early adult	14									
<18.5		2931	918	0.94 (0.86–1.03)	102	0.94 (0.74–1.19)	243	0.93 (0.80–1.09)	164	1.08 (0.83–1.39)
18.5–24.9 (ref)		12 364	4161	1.0	465	1.0	1121	1.0	648	1.0
25–29.9		1151	401	1.04 (0.92–1.18)	54	1.20 (0.88–1.64)	150	1.33 (1.10–1.62)	64	1.05 (0.75–1.45)
30–34.9		231	73	1.03 (0.78–1.37)	19	1.90 (1.12–3.21)	39	1.51 (1.03–2.21)	14	1.10 (0.61–1.99)
≥35		110	36	1.15 (0.75–1.76)	7	2.18 (0.96–4.95)	18	1.85 (1.05–3.24)	6	2.73 (1.08–6.88)
Per 5 kg/m^2[c]				1.02 (0.95–1.10)		1.22 (1.07–1.40)		1.14 (1.04–1.25)		1.02 (0.89–1.16)

*Significant heterogeneity noted (*P* value for heterogeneity <0.05).
[a]Stratified by age in 5-year groups and adjusted for parity (0, 1, 2, 3, 4+ full-term births), hormonal contraceptive use (0, ≤60 and >60 months), family history of breast or ovarian cancer in a first-degree relative and, where appropriate, race/ethnicity; pooled across study sites using random effects models.
[b]Numbers may not sum to total because of missing data.
[c]Excludes women in the underweight range (BMI <18.5 kg/m^2).

analysis to include only studies that assessed weight around 5 years prior to diagnosis to reduce potential bias due to recent weight loss in cases. Considering all non-serous invasive cancers together, the association with recent BMI remained significant after adjusting for maximum BMI or BMI in young adulthood, however after adjusting for recent BMI there was no association with either maximum BMI (OR=1.02, 95% CI 0.95–1.11 per 5 kg/m^2) or BMI in young adulthood (OR=0.96, 95% CI 0.86–1.08 per 5 kg/m^2).

Increasing BMI (all BMI variables) was associated with increased risks of both borderline serous and mucinous ovarian cancers, with significant trends with increasing BMI that were stronger for borderline serous cancers (20–25% increase per 5 kg/m^2) than borderline mucinous cancers (9–11% per 5 kg/m^2; Table 4).

Although there was some heterogeneity among studies for some of the pooled estimates, heterogeneity for the estimates per 5 kg/m^2 only reached statistical significance for recent BMI and risk of clear cell tumours and the combined group of all invasive tumours; sensitivity analyses by study design features suggested that no single factor could explain this observed heterogeneity.

When we combined all tumour types and stratified by ever use of HRT, we observed a significant association between BMI and cancer risk among women who had not used HRT (OR per 5 kg/m^2=1.10; 95% CI 1.07–1.14) but no association among women who had used HRT (1.02; 0.97–1.07). However, we saw markedly different patterns of association when we considered pre- and post-menopausal women and the different histological subtypes of cancer separately (Table 5). When we stratified by menopausal status and use of HRT, we saw significant interaction for recent BMI and risk of invasive serous cancers ($P \leq 0.001$). A significant trend of increasing risk with increasing BMI was observed in pre-menopausal women, with no association among post-menopausal women who had never used HRT, and a significant inverse association among those who had used HRT. Further stratification of the pre-menopausal group suggested that the positive association was stronger for G1 (OR=1.34, 95% CI 1.14–1.59) but still statistically significant for G2–G4 tumours (OR=1.07, 95% CI 1.00–1.15; $P<0.05$). A similar pattern was seen in analyses of maximum BMI and BMI in young adulthood (data not shown), suggesting that the lack of a positive association among post-menopausal women was not simply an artefact due to recent weight loss among women with serous cancer. For all other invasive subtypes combined, the association was somewhat stronger among pre-menopausal women than

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Table 4 Adjusted[a] pooled ORs (95% CIs) for borderline ovarian cancer in relation to BMI, by histological subtype.

			Serous[b]		Mucinous[b]	
	Studies (*n*)	**Controls** (*n*)	Cases (*n*)	pOR (95% CI)	Cases (*n*)	pOR (95% CI)
Recent BMI	10					
<18.5		281	23	1.12 (0.70–1.79)	33	1.61 (1.08–2.39)
18.5–24.9 (ref)		6599	568	1.0	454	1.0
25–29.9		3930	403	1.40 (1.22–1.62)	234	1.08 (0.91–1.28)
30–34.9		1741	236	1.86 (1.55–2.24)	122	1.32 (1.05–1.67)
35–39.9		672	101	2.11 (1.66–2.70)	41	1.29 (0.91–1.84)
≥40		486	85	2.23 (1.69–2.94)	41	1.68 (1.16–2.43)
Per 5 kg/m^2[c]				1.24 (1.18–1.30)		1.09 (1.02–1.16)
Maximum BMI	7					
18.5–24.9 (ref)		2548	135	1.0	138	1.0
25–29.9		2409	153	1.39 (1.00–1.93)	113	0.99 (0.75–1.30)
30–34.9		1236	115	2.00 (1.51–2.65)	78	1.39 (0.99–1.96)
35–39.9		544	66	2.40 (1.71–3.38)	35	1.26 (0.68–2.32)
≥40		455	71	2.73 (1.92–3.88)	30	1.29 (0.79–2.11)
Per 5 kg/m^2[c]				1.25 (1.17–1.34)		1.09 (0.98–1.21)
BMI early adulthood	12					
<18.5		2718	222	0.90 (0.77–1.06)	171	1.07 (0.88–1.31)
18.5–24.9 (ref)		11 245	1034	1.0	699	1.0
25–29.9		983	152	1.40 (1.12–1.74)	86	1.22 (0.95–1.55)
30–34.9		210	40	1.48 (1.03–2.14)	26	1.57 (1.00–2.47)
≥35		100	29	2.34 (1.47–3.74)	12	2.00 (1.00–4.01)
Per 5 kg/m^2[c]				1.22 (1.12–1.33)		1.11 (0.99–1.24)

[a]Stratified by age in 5-year groups and adjusted for parity (0, 1, 2, 3, 4+ full-term births), hormonal contraceptive use (0, ≤60 and >60 months), family history of breast or ovarian cancer in a first-degree relative and, where appropriate, race/ethnicity; pooled across study sites using random effects models.
[b]Numbers may not sum to total because of missing data.
[c]Excludes women in the underweight range (BMI <18.5 kg/m^2).

post-menopausal women but did not differ by HRT use among post-menopausal women. The association with borderline tumours did not vary by menopausal status or HRT use. When we stratified by age at diagnosis (<50 and ≥50 years) instead of menopausal status the results did not differ materially (data not shown).

Discussion

The results of our pooled analysis confirm that being overweight or obese is associated with an overall increased risk of both invasive and borderline ovarian cancers, however for invasive cancers this association appears to be restricted to the non-serous and low-grade serous subtypes. Furthermore, most of our risk estimates were very consistent with those from a previous pooled analysis (Collaborative Group on Epidemiological Studies of Ovarian Cancer 2012) with a strong increase in risk of borderline serous cancer (pOR/RR=1.24 per 5 kg/m^2 in our analysis vs 1.29 in the previous report) and intermediate risks for clear cell (1.06 vs 1.05) and invasive (1.19 vs 1.15) and borderline (1.09 vs 1.06) mucinous cancers. Like the previous report, we saw no increase in risk of invasive serous cancer overall (0.98 vs 1.00), however we did see an increased risk of low-grade invasive serous cancers (OR=1.13) which are now thought to arise via a different aetiological pathway from their high-grade counterparts. The only subtype for which our results differed appreciably was invasive endometrioid cancers where we saw a 17% increase in risk per 5 kg/m^2 overall, and a 25% increase after excluding high-grade endometrioid cancers which are likely to be misclassified as serous tumours (Gilks & Prat 2009), compared with only an 8% increase in the previous study (Collaborative Group on Epidemiological Studies of Ovarian Cancer 2012).

Since endometrioid ovarian tumours are histologically similar to endometrial cancer (Russell 1994), which is strongly associated with obesity (Crosbie *et al.* 2010), it seems plausible that obesity might also be a relatively strong risk factor for this subtype of ovarian cancer. The roughly 70–80% risk increases we observed even among the groups of women with highest BMI were, however, considerably lower than the ninefold risk previously reported for endometrial cancer (Crosbie *et al.* 2010). Historically, the histopathological classification of ovarian cancer cell types has only been modestly reproducible

(Hernandez *et al*. 1984, Cramer *et al*. 1987, Sakamoto *et al*. 1994), and particularly problematic was the specific diagnosis of serous vs endometrioid carcinomas (Stalsberg *et al*. 1988). A recent development is the recognition that many carcinomas formally considered high-grade endometrioid are better classified as high-grade serous (Gilks & Prat 2009, Kobel *et al*. 2010, Madore *et al*. 2010). When we excluded high-grade endometrioid tumours from our analysis the associations with BMI were considerably strengthened while, as for invasive serous cancers, we saw no association with high-grade endometrioid tumours. It is thus possible that misclassification of serous and endometrioid tumours may explain, in part, why a significant association between obesity and endometrioid ovarian cancers has not previously been consistently reported and why it was not observed in the previous large pooled analysis which included mostly older studies and did not consider tumour grade (Collaborative Group on Epidemiological Studies of Ovarian Cancer 2012). Time trends in the use of various regimens of HRT, as well as the increasing prevalence of obesity over calendar time, may also play a role.

As in the previous pooled analysis, we observed an association between increasing BMI and risk of borderline ovarian tumours, with the strength of the association somewhat stronger for serous than mucinous tumours. High BMI has been associated with benign ovarian tumours (Jordan *et al*. 2007), and there is evidence from epidemiological, histopathological and molecular studies that these borderline tumours may develop from benign tumours in a neoplastic progression (Jordan *et al*. 2006). Our finding that low-grade but not high-grade invasive serous tumours were also associated with BMI supports this theory of progression for low-grade serous cancers.

We can only speculate as to why we observed heterogeneity in the association between BMI and risk of invasive serous tumours between pre- and post-menopausal women, however this could not be explained by a higher proportion of G1 tumours in the pre-menopausal group. The endocrine consequences of obesity may have differential effects on the pathogenesis of serous ovarian cancer in pre- and post-menopausal women. Whilst post-menopausal obesity is associated with higher levels of endogenous oestrogen due to the synthesis of oestrogen in body fat (Key *et al*. 2001), in pre-menopausal women, obesity lowers sex hormone-binding globulin (Key *et al*. 2001, Tworoger *et al*. 2006) but does not significantly influence the levels of oestrogens and androgens as the

Table 5 Adjusted[a] ORs (95% CIs) for ovarian cancer in relation to recent BMI, by menopausal status and use of HRT.

		Invasive serous[b]		All other invasive cancers[b]		All borderline [b]	
	Controls (*n*)	Cases (*n*)	OR (95% CI)	Cases (*n*)	OR (95% CI)	Cases (*n*)	OR (95% CI)
Pre-menopausal women							
18.5–24.9 (ref)	2049	484	1.0	514	1.0	529	1.0
25–29.9	919	272	1.23 (1.03–1.47)	275	1.26 (1.06–1.51)	254	1.22 (1.02–1.46)
30–34.9	417	121	1.21 (0.96–1.54)	139	1.40 (1.11–1.76)	147	1.63 (1.30–2.05)
35–39.9	152	55	1.50 (1.07–2.10)	76	1.78 (1.30–2.45)	65	2.00 (1.44–2.78)
≥40	136	47	1.43 (0.99–2.06)	72	1.81 (1.30–2.52)	52	1.76 (1.22–2.53)
Per 5 kg/m^2[c]			1.11 (1.04–1.18)		1.17 (1.11–1.24)		1.19 (1.12–1.27)
Post-menopausal women, no HRT							
18.5–24.9 (ref)	1343	652	1.0	347	1.0	157	1.0
25–29.9	1054	425	0.87 (0.74–1.01)	312	1.20 (1.00–1.43)	124	1.17 (0.90–1.51)
30–34.9	522	216	0.93 (0.77–1.12)	153	1.24 (0.99–1.55)	82	1.60 (1.19–2.16)
35–39.9	226	87	0.89 (0.67–1.16)	67	1.24 (0.91–1.69)	30	1.36 (0.88–2.09)
≥40	157	61	0.87 (0.63–1.21)	65	1.64 (1.18–2.29)	33	2.12 (1.37–3.29)
Per 5 kg/m^2[c]			0.97 (0.92–1.03)		1.10 (1.03–1.17)		1.17 (1.08–1.27)
Post-menopausal women who used HRT							
18.5–24.9 (ref)	1650	778	1.0	313	1.0	138	1.0
25–29.9	1123	440	0.86 (0.75–1.00)	221	1.08 (0.89–1.31)	112	1.35 (1.03–1.76)
30–34.9	480	183	0.86 (0.71–1.05)	101	1.19 (0.92–1.54)	60	1.64 (1.18–2.28)
35–39.9	167	75	1.08 (0.78–1.45)	31	1.15 (0.76–1.74)	20	1.67 (1.00–2.78)
≥40	111	23	0.49 (0.30–0.77)	31	1.64 (1.06–2.52)	13	1.48 (0.80–2.76)
Per 5 kg/m^2[c]			0.92 (0.87–0.98)		1.09 (1.01–1.18)		1.16 (1.05–1.28)

[a]Stratified by study site (AUS, DOV, HOP, MAY, NEC, NJO, UCI and USC) and age in 5-year groups, and adjusted for parity (0, 1, 2, 3, 4+ full-term births), hormonal contraceptive use (0, ≤60 and >60 months), family history of breast or ovarian cancer in a first-degree relative.
[b]Numbers may not sum to total because of missing data.
[c]Excludes women in the underweight range (BMI <18.5 kg/m^2).

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ovaries produce more steroids than the peripheral fat tissue. Other hormonal factors that may mediate the relationship between obesity and risk of ovarian cancer include progesterone (Risch 1998) and insulin (Calle & Kaaks 2004). Compared with women of 'normal' weight, pre-menopausal obese women have reduced serum progesterone levels due to an increase in anovulatory cycles (Key *et al*. 2001), and there is a significant body of evidence suggesting that progesterone plays a protective role in ovarian carcinogenesis (Risch 1998). Obesity is associated with increased insulin levels, which lead to increases in the insulin-like growth factor 1 (IGF1; Calle & Kaaks 2004). There is no clear relation between adiposity and IGF1, however high levels of IGF1 have been associated with ovarian cancer in women younger than 55 years of age (Lukanova *et al*. 2002).

Our observation that the positive association with BMI was stronger among pre-menopausal women is consistent with the earlier analysis of cohort studies (Schouten *et al*. 2008). However, in contrast to the recent pooled analysis (Collaborative Group on Epidemiological Studies of Ovarian Cancer 2012), we found no suggestion of effect modification by use of HRT in post-menopausal women. Although the overall association did appear to be restricted to women who had never used HRT, this was driven by the stronger associations seen among pre-menopausal women who rarely use HRT. Similarly, the apparent lack of association among HRT users was driven by the strong inverse association with invasive serous cancers, the most common histological subtype, in this group. For the cancers that showed an overall association with BMI, non-serous invasive and borderline cancers, the risk estimates among post-menopausal women did not differ by use of HRT. Whilst data on recent or current use of menopausal hormonal therapy were not available for the current analyses, the possibility that recent use may modify the relationship between BMI and ovarian cancer risk deserves further exploration.

Strengths of our study include the large number of cases and controls made possible by pooling data from 15 individual case–control studies. Individual-level data were combined into a single dataset following a rigorous data cleaning and harmonisation protocol, giving enhanced ability to control for confounding in individual studies (Stukel *et al*. 2001). Pooling these data increased our statistical power to examine BMI in relation to the different histological subtypes of ovarian cancer, and allowed subgroup analyses to examine the effects by tumour grade, age, menopausal status, and for post-menopausal women, by use of HRT. Additionally, all studies contributing to the pooled analyses were conducted in the past two decades and, aside from early cases from the NEC and USC studies, a total of ~1200 cases (10%), there was no overlap with the previous pooled analysis (Collaborative Group on Epidemiological Studies of Ovarian Cancer 2012). Histological misclassification is likely to be considerably less of a concern for these recent studies than in studies conducted in the more distant past, although some degree of misclassification remains likely.

However, as with any pooled analysis, some limitations must be acknowledged. First the majority of the studies included in the pooled analyses relied upon retrospective self-reports of weight and height. Research has shown that women with higher BMI are more likely to underestimate weight, whereas underweight women are more likely to overestimate body weight (Kuskowska-Wolk *et al*. 1989, Troy *et al*. 1995, Lawlor *et al*. 2002, Taylor *et al*. 2006); this may have attenuated the true associations. We cannot exclude the possibility of selection bias due to self-selection of more health conscious women, who are less likely to be overweight or obese, into control groups; this would have lead to overstated risk estimates. Such misclassification, however, is likely to be non-differential with respect to the different histological subtypes. Finally, weight loss several years before the time of cancer diagnosis would, if present, bias risk estimates towards the null although the similar patterns of risk seen for all three measures of BMI, and for analyses of recent BMI restricted to studies that asked women to report their usual weight ~5 years prior to diagnosis, suggest that this has not occurred to any great extent.

In summary, obesity appears to moderately increase the risk of developing the less common histological subtypes of ovarian cancer, particularly borderline and low-grade invasive serous cancers and endometrioid cancers. With the possible exception of pre-menopausal women, it does not, however, appear to increase risk of the more common high-grade invasive serous cancers that account for the majority of ovarian cancer deaths.

Supplementary data

This is linked to the online version of the paper at http://dx.doi.org/10.1530/ERC-12-0395.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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